CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
10,10'-OXYBISPHENOXARSINE

Chemical Code # 001402, Tolerance # 50233
SB 950 # 163
September 5, 2003

I. DATA GAP STATUS

Chronic Toxicity, rat:	Data gap, no study on file
Subchronic, rabbit dermal	Data gap, possible adverse effects (dermal and systemic)
Chronic Toxicity, dog:	Data gap, no study on file
Oncogenicity, mouse:	Data gap, no study on file
Oncogenicity, rat:	Data gap, no study on file
Reproduction, rat:	Data gap, no study on file
Teratology, rat:	Data gap, inadequate study, no adverse effect indicated
Teratology, rabbit:	Data gap, no study on file
Gene mutation:	Data gap, study inadequate, no adverse effect indicated
Chromosome:	Data gap, no study on file
DNA damage:	Data gap, no study on file
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T030905
Original by: J. Kishiyama and J. Gee, September 5, 2003

OBPA is classified as an antimicrobial with only non-food uses. The uses registered in California are as preservatives in plastics. The US EPA issued a "Reregistration Eligibility Document (RED)" in June of 1993. At that time, the Agency was not requiring any additional toxicity studies of the types required under SB950 or related studies (e.g., subchronic studies) for antimicrobials. See the note on page 5 regarding an oral subchronic study not on file with DPR.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

No study submitted.

CHRONIC TOXICITY, RAT

No study submitted.

CHRONIC TOXICITY, DOG

No study submitted.

ONCOGENICITY, RAT

No study submitted.

ONCOGENICITY, MOUSE

No study submitted.

REPRODUCTION, RAT

No study submitted.

TERATOLOGY, RAT

017 115354 Beliles, R. P. "Teratology Study in Rats: 10,10'-Oxybisphenoxarsine." (Litton Bionetics, Inc., LBI Project No 20816, April 1978.) 10,10'-Oxybisphenoxarsine (batch IC-001-087, 95.6%) was administered by dermal application at doses of 0, 0.3, 3 and 30 mg/kg to 20 mated female Sprague-Dawley rats/group on Days 6 through 15 of gestation. The application site was not occluded so that some oral ingestion may have occurred, making effects from dermal absorption difficult to distinguish from oral effects. Mortality was 100% between days 10 and 14 at the high dose, before scheduled sacrifice. Body weights and weight gains were lower for all 10,10'-oxybisphenoxarsine treatment groups. Maternal NOEL < 0.3 mg/kg/day. Live Fetuses/Implantation Site was lower at 0.3 mg/kg/day (91%) compared with control of 96% with a Fetal NOEL < 0.3 mg/kg/day. There was no reported evidence of teratogenicity. UNACCEPTABLE (major variances and insufficient information). Not Upgradeable. (Kishiyama and Gee, 9/2/03).

004 024190 Summary of 115354.

TERATOLOGY, RABBIT

No study submitted.

GENE MUTATION

017 115352 Brusick, D. J. "Mouse Lymphoma Mutagenicity Evaluation of 10,10'-Oxybisphenoxarsine." (Litton Bionetics, Inc., LBI Project No. 2548, October 29, 1976.) 10,10'-Oxybisphenoxarsine was tested at concentrations of 0.0005-0.05 μg/ml with and without male mouse liver S9 activation for mutagenicity with mouse lymphoma $TK^{+/-}$ cells. There were two trials with activation and a single trial without activation. Apparently only a single culture was tested. There was a significant increase in mutation frequency in the initial assay at concentrations of 0.001 and 0.01 but not at 0.005 μg/ml. This finding was not repeated with 10,10'-Oxybisphenoxarsine exposure in the second trial. Results in the single trial without activation were negative. The author concluded the increase in mutation frequency observed initially was an aberrant effect and based on overall study results, 10,10'-oxybisphenoxarsine was not mutagenic to mouse lymphoma cells. Based on the limited data given in the summary tables, an independent evaluation could not be made. UNACCEPTABLE (insufficient information including lack of purity, lack of individual plate counts, missing details of study conduct). Not upgradeable (inadequate number of trials). (Kishiyama and Gee, 8/26/03).

004 024192 Interpretation and conclusion section (page 5) of 017 115352.

017 115353 Brusick, D. J. "Mutagenicity Evaluation of 10,10'-Oxybisphenoxarsine (Technical) ." (Litton Bionetics, Inc., LBI Project No. 2547, June 18, 1976.) 10,10'-Oxybisphenoxarsine was tested at concentrations of 0.0005 to 2.5μg/plate with and without Aroclor 1254-induced male rat liver S9 activation for mutagenic effect using *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 and *Saccharomyces cerevisiae* strain D4. There was one trial with 5 concentrations ± activation, apparently a single plate per concentration. From the summary data, there was no significant increase in the number of revertants with 10,10'-Oxybisphenoxarsine treatment. The solvent control for TA98 without activation had 196 revertants but the author did not discuss this finding. There was little evidence of toxicity in the presence of S9 in any strain at 2.5 ug/plate. UNACCEPTABLE (insufficient information, single plate per strain per concentration). Not upgradeable. (Kishiyama and Gee, 8/26/03).

004 024191 Interpretation and conclusion section (page 5) of 017 115353.

017 115354 Jagannath, D. R. "Teratology Study in Rats 10,10'-Oxybisphenoxarsine." (Litton Bionetics, Inc., LBI Project No 20816, April 1978.) The urine from rats treated with 10,10'-Oxybisphenoxarsine (0.3, 3 and 30 mg/kg on Days 6 through 15 of gestation) by the dermal route was evaluated for mutagenicity using *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98, and TA 100 without S9. Urine was collected on days 6, 9, 16 and 20 of gestation. Aliquots of 0.1, 0.2 and 0.3 were tested with each strain for each day. No S9 mix was used. A portion of the urine was pretreated with β-glucuronidase before assay. No evidence of the production and/or excretion of mutagenic metabolites was reported. SUPPLEMENTAL STUDY. (Kishiyama and Gee, 9/2/03).

CHROMOSOME EFFECTS

No study submitted.

DNA DAMAGE

No study submitted.

MISCELLANEOUS

Subchronic, Rabbit Dermal:

018 115355 Cox, G. E. and K. R. Stevens "Dermal and Systemic Toxicity Study of Vinyzene BP-5 Following Repetitive Dermal Application over a 21 Day Period to the Intact and Abraded Skin of New Zealand Albino Rabbits." (Food and Drug Research laboratories, Inc., Laboratory No. 5801, January 5, 1979.) Vinyzene BP-5 (lot no. 22789, 1% activity) was applied to the skin for 6 hours per day for five days per week for three weeks. During dosing, the rabbits were placed in stocks. Doses were 0 (Eso & Nonyl Phenol Mix), 0.1, 0.5 or 1.0 g/kg (reduced to 0.75 on Day 13 of the test due to mortality). The report did not state whether the test article (Vinyzene BP-5, a gelatinous material) was diluted or applied neat or what volumes were applied per animal per dose. There were 10 males and 2 females in the controls, 5 males and 7 females at 0.1 g/kg, 6/sex at 0.5, and 9 males and 3 females at 1.0 g/kg. The excess of males in the control and high-dose groups was to investigate the potential for testicular toxicity. Also, several animals were incorrectly identified as to sex. The skin of a portion of the animals was abraded. Nasal discharge and decreased activity were reported for treated groups. Mortality: None in the controls and low dose groups. At 0.5 g/kg (3/6 males and 1/6 females) and 1.0 g/kg (6/10 males and 3/3 females) animals died or were sacrificed moribund. Causes of death included pneumonia and death from blood sampling via cardiac puncture (to obtain 20 ml of blood for hematology and biochemical assays pretest and at 21 days) as well as unknown reasons. A portion of each group were held for an additional 4 weeks after dosing for recovery (3, 3, 1, and 1 males and 0, 3, 3, and 0 females). There were no effects on hematology, clinical chemistry, urinalysis or ophthalmology of toxicological concern. Dermal scores for erythema reached 4.00 (Draize method of scoring) by day 4 of dosing in all treated groups compared with a score of 2.9 in male and 2.5 in female controls. The vehicle alone caused significant erythema and edema in both sexes. Scores for erythema in treated males continued to be significant during the recovery period. Edema was significantly increased in all treated groups on day 1 and continued through the dosing period. Scores decreased during the recovery period in males. Female scores in the recovery period were not reported due to lack of surviving control animals. Histopathology of the testes verified treatment-related effects at 0.5 and 1.0 g/kg. Findings included decreased spermatogenesis, atrophy and degeneration (2/10, 2/5, 3/6 and 7/10) with increasing dose with scores of 0.65, 1.5, 1.67 and 2.14, controls through high dose (scoring not defined). Every other page of the individual data was missing. Other effects related to treatment included skeletal muscle changes (4 mid-dose males, 6 high-dose males and 2 females) and focal hemorrhages (capillary fragility), especially at 1.0 g/kg. The authors attributed some findings to stress. **Possible adverse effects**. Dermal NOEL < 0.1 g/kg (equivalent to 1 mg/kg 10,10'-oxybisphenoxyarsine?). Systemic NOEL possibly 0.1 g/kg (testicular effects, focal hemorrhages) but unclear from the data presented. UNACCEPTABLE (major deficiencies). Not upgradeable (dose selection, inadequate number of animals, methods used, high mortality, others). (Kishiyama and Gee, 9/5/03)

002 029297 Palazzolo, R. J. "Repeated Dermal Toxicity of Vinyzene BP-5." (Industrial Bio-Test Laboratories, Inc., November 21, 1964.) Vinyzene BP- 5 was applied undiluted at doses of 1.0 or 2.0 g/kg to the skin (abraded and intact) of the backs of 5 New Zealand albino rabbits/sex/group for 21 days (7 hours/day, 5 days/week for a total of 15 doses), apparently

nonoccluded. Limited parameters were examined for hematology, clinical chemistry and urinalysis. Approximately 10% of the body surface was used. Mortality was 85% and 10% for the high-dose and low-dose groups, respectively. There was body weight loss occurred in the high-dose group. Animals in both dose groups exhibited severe inflammatory reactions at the site of application, being characterized by erythema, edema, subdermal hemorrhages, wrinkling, drying and cracking. The first signs appeared after 2 or 3 doses. Dermal NOEL < 1 g/kg/day. UNACCEPTABLE (Limited parameters for hematology and clinical chemistry, no individual histopathology data, others). **Status of audit unknown**. No worksheet. (Kishiyama and Gee, 8/20/03).

Subchronic rats:

003 029312 Morrow, L. and J. C. Calandra. "90-Day Subacute Oral Toxicity with Vinyzene in Albino Rats." (Industrial Bio-Test Laboratories, Inc., IBT No. 8560-08838, September 27, 1976.) Vinyzene® SB-1 was admixed with the feed at concentrations of 0, 5000, 10000, or 50000 ppm and fed for 90 days to 15 albino rats/sex/group. IBT Tracking System Report validation process determined this study as **INVALID** (replacement study under discussion). No worksheet. (Kishiyama and Gee, 8/20/03).

NOTE: The following study was cited by US EPA in the RED of 1993 but is not on file with the Department of Pesticide Regulation in California as of this date.

McCollister, S. B., G. L. Sparschu and H. C. Spencer, "Results of 92-day dietary feeding studies on OBPA in rats." Study prepared by Biochemical Research Laboratory, Dow Chemical Co., 1969.

OTHERS

50233 - 017 115349 "The comparative short-term mammalian toxicology of phenarsazine oxide and phenoxarsine oxide." (Ballantyne, B., publ. in *Toxicology* 10: 341-361 (1978)) Phenoxarsine oxide (PXO) and phenarsazine oxide (PZO) were tested for acute effects by the oral, inhalation and dermal routes. The purity of the test articles was not stated. In addition, subacute (30 days) exposure, skin irritation, skin absorption and eye effects were also examined. Animals used were male Porton-Wistar rats, male Duncan Hartley guinea pigs and female New Zealand White rabbits. Acute oral toxicity: Ten rats per dose were given PXO in vehicle (0.5% Triton X-100 and 0.5% carboxymethyl cellulose) at seven doses ranging from 25 to 100 mg/kg and ten guinea pigs were given doses ranging from17.7 to 100 mg/kg. Those dying and the survivors at three weeks were examined for histological changes in the lung, liver, kidney, stomach and small intestines. The LD_{50} for male rats was 40 mg/kg (95% confidence range of 36 - 45) and for male guinea pigs, 24 mg/kg (range of 22 to 26). Clinical signs seen at sublethal doses included pilo-erection, agitation on handling, abdominal tenseness and sluggish movement within a few hours of dosing. Between the second and tenth days, decreased muscle tone, increased rate and depth of breathing were seen, disappearing by the 14^{th} day. Histological exams of guinea pigs were normal for those tissues examined. Rats surviving for 21 days showed a slight increase in portal tract mononuclear cells (no data). Those rats dying showed edema, bile duct proliferation and mid- and peri-portal necrosis of the liver, dose-dependent changes in the lung, and congestion and hemorrhagic erosions of the gastrointestinal tract. Hepatotoxicity: 20 rats were given 30 mg/kg PXO in Triton X-100-CMC by gavage. Two rats were sacrificed at 1, 6 and 24 hours and 2, 3, 4, 7, 10, 14 and 21 days. Blood was sampled for bilirubin and liver sections stained for histology. Results were compared with vehicle controls. Serum bilirubin doubled within 24 hours in treated

rats, remaining elevated for 5 days, returning to normal levels by day 7. Histology was normal at all intervals. Acute inhalation toxicity: Male guinea pigs, 5 per group, were exposed to a 10% suspension of PXO in water for a series of 10 dosages (mg min/m^3), obtained by varying the time of exposure and the atmospheric concentration. Mortality over 14 days was recorded. Dosages ranged from 5000 to 16,900 mg min/m^3. The $L(ct)_{50}$ was 12,829 (range 11,246 - 17,292). All deaths occurred within 24 hours. At higher concentrations for 1 hour or longer, clinical signs of nasal discharge, restlessness, pilo-erection and increased breathing rate were noted, subsiding in 24 - 48 hours. At autopsy, animals showed gross pulmonary congestion and hemorrhage with patches of edema. Subacute inhalation toxicity: Rats and guinea pigs, 25 of each, were exposed to PXO at 1 - 2 mg m^3 for 30 consecutive days, 5 hours per day, for a cumulative dosage of 14,531 mg min m^{-3}, approximately equal to the $L(ct)_{50}$ of a single dose. Half were sacrificed 48 hours after the final exposure and the remainder at 4 months. Body weights were recorded and the lung, liver and kidney examined for histological changes. No deaths occurred and no signs were noted. Body weight gain for rats and guinea pigs was similar to controls. Animals sacrificed at 48 hours after dosing ended showed mild to moderate alveolar capillary congestion with a few intra-alveolar hemorrhages. Livers from guinea pigs were normal but rat livers showed mild to moderate increases in portal tract mononuclear cells. At 4 months, livers of both species were normal. Skin irritation: A 0.2 ml aliquot of a 25% suspension of PXO in 0.5% Triton X-100 and 0.5% CMC (50 mg) was applied daily for 6 hours for 5 successive days to the shaved dorsal skin (1.5 cm in diameter) of 6 guinea pigs. The area was covered. After dosing, the area was washed with water. After the first application, slight skin thickening occurred; after the second, 5/6 also showed erythema; after the third and fourth, well-defined thickening and erythema with escharosis in the area of application and after the fifth, the escharosis became confluent. Two days after the final dosing, well-defined eschar was present but after 9 days, only minor scarring was noted. No effects were noted with the vehicle control. Percutaneous absorption: PXO, 20% suspension in corn oil, equivalent to 100 mg, was applied in 0.5 ml to the clipped skin of 3 guinea pigs for 6 hours, then animals were sacrificed. Dose was approximately 300 mg/kg. Blood was collected and the liver and kidney removed, weighed and digested for analysis of arsenic, with a detection of 15 ug of As or 50 ug of PXO. No As was detected in blood, liver or kidney. Ophthalmic toxicology: 6 rabbits/group were given doses of PXO in PEG300-5% DMSO of 0.5, 0.25 or 0.1% (w/v) in 0.1 ml in the conjunctival sac of the right eye. Solvent controls were included. Eyes were inspected at 10 minutes, 1 hour and daily for up to 21 days. Effects were scored on a 60 point scale of 0 = no effect to 5 = severe with complications. Attention was paid to lachrymation, blepharitis, injection of the conjunctival vessels, chemosis, iritis and keratitis. At the end of the test period, the eyes were removed and examined for histological changes. Effects were: 0.5%: Within 1 hour, mild blepharitis and moderately severe lachrymation, chemosis and injection appeared, resolving slowly but still detectable in 2 animals at 3 weeks. At 24 hours, multiple hemorrhages in conjunctiva and nictitating membrane were noted with necrosis at 4 days. Hemorrhages and necrosis resolved by 10 days. Other effects (mild keratitis, corneal neovascularization) were also noted during the observation period. Histology at 2 weeks showed increased corneal thickness with undulant deformity, patchy denudation of epithelium and other changes. Saline irrigation shortly after application did not alter the nature, severity or duration of the effects. 0.25%: Mild to moderate conjunctivitis and blepharitis resolved in 7 to 14 days. Just detectable mild keratitis was evident day 1 and still present at 3 weeks. Histology showed slight corneal thickening (0.57 mm, normal range from 6 rabbits 0.34 - 0.39 mm) but epithelium appeared normal with only a few foci of neutrophil infiltration in the outer half of the substantia propria. 0.1%: Just detectable lachrymation, blepharitis, conjunctival injection and chemosis at 1 hour, persisting for 2 - 3 days. Histological appearances were normal. PXO in PEG300 alone gave results "identical" to the combined vehicle. Intraocular pressure was measured after exposure to 0.25, 0.1, 0.05, and 0.01% PXO in PEG-DMSO, 0.1 ml in the conjunctival sac, and

measured 10 and 60 minutes after instillation. Dose-dependent increases were measured at 10 minutes, being significant at all concentrations. The percent increases were 3, 28, 43 and 85 with increasing concentrations at 10 minutes (example: control pressure of 15.66 mm Hg and 28.89 at 0.25%). At 1 hour, pressure at 0.25% could not be measured because of chemosis. At 0.1%, the increase was 33%, compared with 43% at 10 minutes. At 0.1%, pressure was the same as control. Data for PZO were presented in the publication but were not included here. SUPPLEMENTAL STUDY. No worksheet. (Gee, 8/21/03)

50233 - 017 115350 "*In vitro* effects of 10, 10'-oxybisphenoxarsine on isolated rat liver mitochondria." (Kronenberg, J. M. and M. J. Brabec, publ. in *Toxicol. Appl. Pharmacol.* 62: 282 - 287 (1982)) Mitochondria were isolated from the livers of fasted male CD rats. Livers were removed, homogenized and centrifuged at 500 g followed by 7500g to obtain a crude pellet of mitochondria. After washing, the mitochondria were resuspended to give approximately 30 mg of protein per ml. The effect of different concentrations of OBPA, 1 to 8 uM (no impurities detected), on oxygen uptake by several substrates (α-ketoglutarate, isocitrate, pyruvate and succinate) over approximately 8 minutes was determined. Each assay contained 2.3 mg mitochondrial protein plus the various substrates and additional components. Shortly after the addition of excess ADP (4 μmol), the various concentrations of OBPA were added and oxygen uptake determined. OBPA rapidly inhibited state 3 respiration with all 4 substrates, the degree of inhibition depending on the substrate and the OBPA concentration. The inhibition was unaffected by the addition of 2,4-dinitrophenol. When added during state 4 respiration following the addition of 0.2 μmol ADP, OBPA caused an initial increase in oxygen uptake followed by progressive inhibition, the pattern depending on the substrate. There was no effect of 8 μM OBPA on electron transport as measured by NADH oxidation in mitochondria made permeable by swelling. OBPA, 4 μM, was a potent inhibitor of both α-ketoglutarate dehydrogenase and pyruvate dehydrogenase. In addition, OBPA also inhibited both NAD- and NADP-specific isotitrate dehydrogenases in a concentration dependent manner. Glutathione protected α-ketoglutarate dehydrogenase from inhibition by OBPA. The authors concluded that OBPA reacts with mitochondrial sulfhydryl groups. SUPPLEMENTAL STUDY. No worksheet. (Gee, 8/22/03)

50233 - 017 115351 "The disposition of 10-10' oxybisphenoxarsine (OBPA) in rats, rabbits and guinea pigs." (Kronenberg, J. and R. Hartung, publ. in *Drug and Chemical Toxicology* 4: 275 - 281 (1981)) [U-^{14}C]OBPA was given in a single dose to 4 fasted male CD(SD) rats (1.1 mg/kg), 3 male New Zealand White rabbits (1.6 mg/kg) and 4 male Dunkin-Hartley guinea pigs (2.3 mg/kg). Urine and feces were collected daily for 7 days after which the animals were sacrificed and selected tissues analyzed. Approximately 90% was excreted within 7 days in all three species with more being excreted in the feces. In rats, 82% was found in the feces, 59% in rabbit and 57% in the guinea pig. Tissue distribution at day 7 showed that the liver retained the most radioactivity with the exception of the erythrocytes of rats, which retained an estimated 3.4% compared with 0.03% in the rabbit and 0.08% in the guinea pig. SUPPLEMENTAL STUDY. No worksheet. (Gee, 8/25/03).